0022-202X/81/7705-0406$02.00/0
THE JOURNAL OF INVESTIGATIVE DERMATOLOGY, 77:406–409, 1981

Vol. 77, No. 5
Printed in U.S.A.

Impaired Antigen-Specific Suppressor Cell Activity in Psoriasis and Psoriatic Arthritis

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Antigen specific suppressor cell activity of peripheral blood mononuclear cells was investigated in 20 patients with psoriatic arthritis and 18 patients with uncomplicated psoriasis and compared to that of 27 age- and sex-matched healthy controls and 18 patients with osteoarthritis. Topical skin therapy and nonsteroidal anti-inflammatory medications were allowed but patients who had taken disease suppressive, immunosuppressive, cytotoxic, and systemic steroid therapy were excluded.

The results demonstrate reduced suppressor cell activity (SCA) in patients with psoriatic arthritis compared to normal controls (54.8% ± 4.9 vs 68.4 ± 2.8, $p < 0.005$). Similarly, the response of patients with uncomplicated psoriasis was significantly lower than normal (50.1 ± 4.9 vs 67.3 ± 3.0% $p < 0.005$). Five of the 20 patients with psoriatic arthritis and 7 of the 18 patients with uncomplicated psoriasis demonstrated SCA of more than 2 SD below the normal mean.

The SCA of patients with osteoarthritis was normal. The plaque forming cell (PFC) response of patients with psoriatic arthritis and uncomplicated psoriasis was not different from those of the normal controls or of patients with osteoarthritis. There was no correlation between impaired suppression and disease activity or therapy.

Psoriasis is a chronic skin disorder that affects 1–3% of the general population [1]. Up to 30% of the patients with psoriasis may have an associated seronegative arthritis [2,3]. The etiology of psoriasis and psoriatic arthritis remains unclear. Recent evidence suggests that immune mechanisms contribute at least in part to the tissue injury in this disease [4]. Thus, a hyperactive humoral, or B cell response has been demonstrated in association with impaired T cell function [5]. It has been suggested that the humoral immune abberations described in psoriatic patients may result from a loss of T regulatory (suppressor) cells [6]. This concept is supported by studies in autoimmune diseases in which hyperactive B cell function is associated with defective T suppressor cell activity. We have previously demonstrated impaired suppressor cell activity in patients with systemic lupus erythematosus and rheumatoid arthritis [7,8]. In both these disorders a defect in suppressor cell function has been postulated as contributing to autoantibody formation. Recently, impaired suppressor cell function was demonstrated in patients with cutaneous psoriasis [9,10]. We therefore studied suppressor cell function in patients with cutaneous psoriasis and in patients with psoriatic arthritis, using an antigen specific suppressor cell assay [11]. Our study demonstrates impaired antigen specific suppressor cell activity in some patients with psoriasis and psoriatic arthritis relative to healthy controls and patients with osteoarthritis.

Manuscript received December 12, 1980;; accepted for publication April 15, 1981.

This work was supported by grants from the Canadian Arthritis Society and Women's College Hospital Research Fund.

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Abbreviations:
OA: crystalline ovalbumin
PBM: peripheral blood mononuclear cells
PBS: phosphate buffered saline
PERC: Psoriasis Educational and Research Center
PFC: plaque forming cells
SCA: suppressor cell activity
SRBC: sheep red blood cells

MATERIALS AND METHODS

Patient Populations

Psoriasis: 18 patients with cutaneous psoriasis, uncomplicated by arthritis, who were attending the Psoriasis Education and Research Center (PERC), Women's College Hospital, Toronto, were studied (Table). There were 12 females and 6 males with a mean age of 40 yr and a mean disease duration of 14.4 yr. None had taken systemic steroids, methotrexate, PUVA, or Retinoid therapy. Skin assessments were performed by a dermatologist according to a standard protocol and expressed as percent skin involvement.

Psoriatic arthritis: 20 patients attending the Psoriatic Arthritis Clinic and PERC, Women's College Hospital, were studied. There were 12 males and 8 females with a mean age of 52 yr and a mean disease duration of 15.7 yr for skin disease and 10.8 yr for joint disease (Table). None of the patients had taken systemic steroids, disease suppressive (gold, chloroquine, penicillamine), or cytotoxic therapy (Imuran, methotrexate or PUVA), nor Retinoid therapy prior to the study. Medications taken at the time of the study are listed in the Table. Skin disease was assessed by a dermatologist as above, and joint involvement was recorded by a rheumatologist according to the number of actively inflammed joints (stress pain, tenderness, effusion) and articular index. All patients had peripheral joint involvement—while 6 had both peripheral and axial joint disease.

Controls

(a) Healthy volunteers (hospital personnel) age- and sex-matched to the patients constituted the normal controls. (b) Eighteen patients with radiologically defined erosive osteoarthritis were also studied. There were 14 females and 4 males with a mean age of 63 yr. All were taking nonsteroidal anti-inflammatory medications at the time of the study.

Cell Separation

Peripheral blood mononuclear cells (PBM) were isolated by Ficoll-Hypaque gradient centrifugation [12]. The cells were then washed twice with phosphate buffered saline (PBS), pH 7.4 and resuspended in RPMI 1640 (Gibco, Grand Island, New York), supplemented with alpha glutamine (2 mM), 2-mercaptoethanol (5×10^{-5} M) penicillin (100 u/ml), streptomycin (10 μg/ml) and 10% heat-inactivated normal human serum.

Antigen

Crystalline ovalbumin (OA) (Sigma Chemical Company, St. Louis, Missouri) was prepared as a stock solution (1 mg/ml) in PBS and stored at −20°C. Sheep red blood cells (SRBC) (Woodlyn Farms, Guelph, Ontario) were washed 3 times before use.

Complement

Commercially available guinea pig complement (Gibco, USA) was reconstituted and absorbed 3 times with SRBC.

Clinical data

	Psoriasis	Psoriatic arthritis
Number of patients	18	20
Male/female	6/12	12/8
Mean Age in years (range)	40(21–76)	52(24–70)
Mean Disease Duration		
Skin (range)	14.4(1–39)	15.7(3–40)
Joints (range)	—	10.8(0.2–35)
Number untreated	8	8 Skin 5 Joints
Topical agents		
Tar	11	12
Steroid cream	6	3
UVB light	11	7
Antirheumatic medications	—	15
Enteric coated ASA	—	9
Indocid	—	3
Other nonsteroidal	—	3

Plague Forming Cell (PFC) Response

PFC were induced and evaluated according to the method of Dosch and Gelfand as previously described [11]. Ten ml target cultures were set up in 17 × 100 mm plastic tissue culture tubes containing 2×10^6 fresh PBM with 10 μg OA (optimal for PFC generation) in supplemented RPMI 1640 media. After 6 days in moist 5% CO_2 at 37° incubation the target cultures were washed twice and assayed in triplicate for PFC. Less than 200 plaques per 10^6 lymphocytes were considered background.

Generation of Suppressor Cells and Suppressor Cell Assay

Suppressor cells were generated by incubating 2×10^6 fresh PBM with 100 μg of OA. Control cells were incubated without OA. After 24 hr the cells were harvested, washed twice with RPMI 1640, and resuspended at a concentration of 1×10^6 cell/ml. Cell viability and recovery of the OA-primed cultures were comparable to control (unprimed) cultures. One million viable OA-primed or control cells were added to a target culture of 2×10^6 fresh autologous cells. The mixture was cultured with 10 μg of OA for 6 days at 37°C, harvested and assayed for direct anti-OA PFC as described. Suppression was expressed as $\left[1 - \frac{\text{PFC(P)}}{\text{PFC(C)}}\right] \times 100\%$ suppression, where PFC(P) was the PFC response when primed cells were added and PFC (C) the response when unprimed (control) cells were added to the target cultures.

Statistical Methods

Student *t*-test was used to compare the degree of suppression between patient and control groups. A regression analysis was used for correlations between degree of suppression and disease activity and between PFC response and disease activity [13].

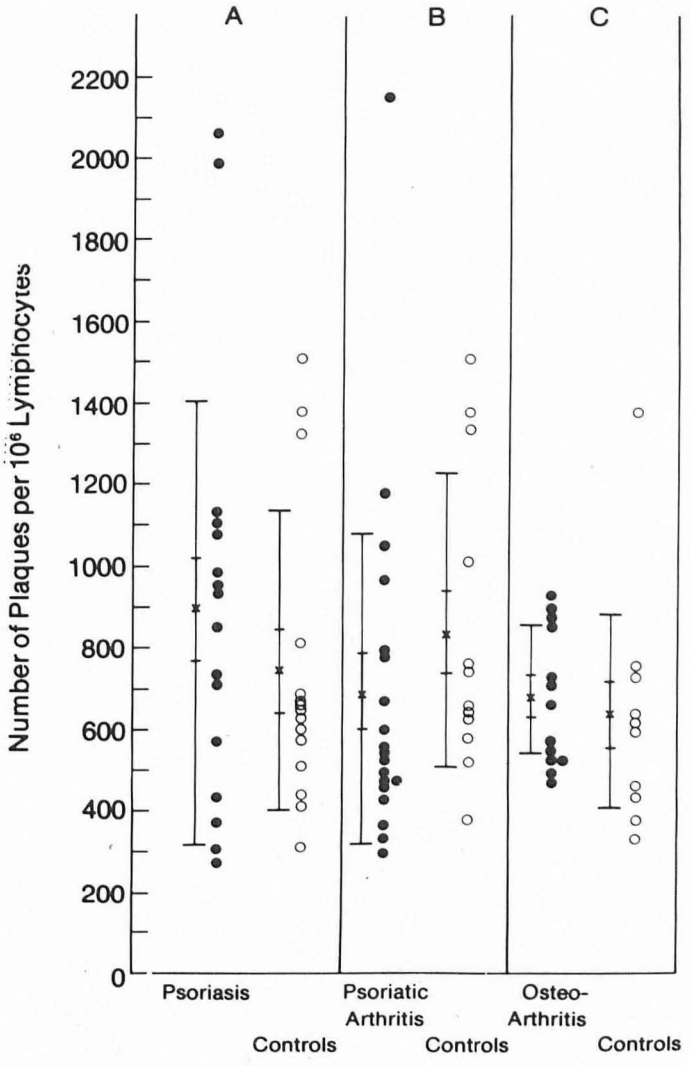

FIG 1. Plaque forming cells (PFC) responses of optimally primed (10 μgm crystalline ovalbumin/culture) target cultures in patients (●) and controls. (○). Each *point* represents the mean PFC response of triplicate cultures. Mean PFC response is depicted by (*X*) and error bars represent ± 1 SE (-) and ± 1 SD (—). *A*, uncomplicated psoriasis; *B*, psoriatic arthritis; and *C*, osteoarthritis.

RESULTS

The *in vitro* plaque cell response to ovalbumin was first examined. Lymphocytes from patients with psoriasis exhibited a higher PFC response than the matched controls, but the difference was not statistically significant (Fig 1*A*). The *in vitro* plaque response of patients with psoriatic arthritis was not different from normal controls or patients with osteoarthritis (Fig 1*B* and *C*). Suppressor cell activity of the 18 patients with cutaneous psoriasis was compared to that of 14 age and sex matched normal controls (Fig 2*A*). The results demonstrated significantly reduced suppression in the patients (50.1 ± 4.9% vs 67.3 ± 3.0%, $p < 0.005$). Seven of the 18 patients or 39.9% demonstrated suppression of less than 2 SD below the normal mean.

Similarly, 20 patients with psoriatic arthritis demonstrated significantly reduced suppressor cell activity when compared to 12 age and sex matched controls (Fig 2*B*). (54.8% ± 4.9 vs 68.5 ± 2.8%, $p < 0.005$). Five of the 20 patients (25%) demonstrated suppression of less than 2 SD below the normal mean.

The antigen specific suppressor cell activity observed in patients with osteoarthritis was not different from that of normal controls (64.9 ± 3.4% vs. 66.6 ± 2.7%; Fig 2*C*). There was no correlation between PFC responses and suppressor cell activity.

The impaired suppressor cell activity observed in patients with psoriasis and psoriatic arthritis did not correlate with either extent of skin disease or with the degree of joint involvement. There was no relationship between the degree of suppression and the pattern or duration of the skin or joint disease.

DISCUSSION

It has been suggested that a defective cellular immune response may lead to the development of psoriasis [4]. Immunological abnormalities have indeed been reported in patients with cutaneous psoriasis and in patients with psoriatic arthritis [4–6, 14–20]. These patients have demonstrated a hyperactive B cell response manifested by increased levels of immunoglobulins, particularly of IgG and IgA classes [14–20]. Recently, circulating immune complexes have been detected in the sera of patients with cutaneous psoriasis and psoriatic arthritis [5,16,21]. *In vitro* studies of T cell-mediated immune functions

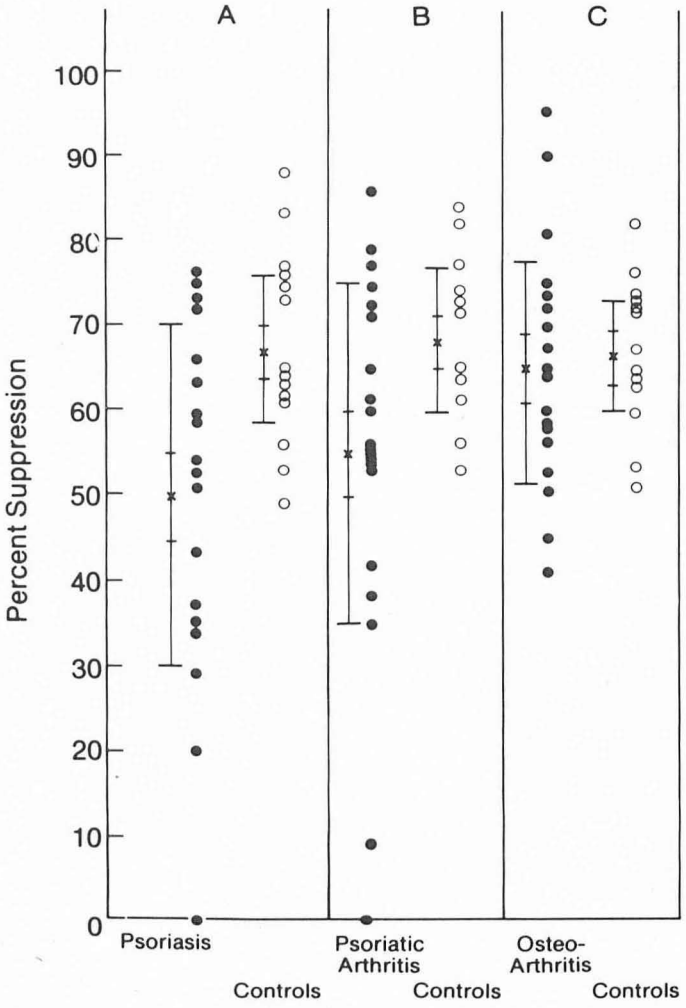

FIG 2. Suppressor cell activity in patients and controls. Each *point* represents percent suppression for the individual patient (●) or control (○). Mean percent suppression for each group is shown (*X*) and the *error bars* indicate ± 1 SE (-) and 1 ± SD (—). *A*, uncomplicated psoriasis; *B*, psoriatic arthritis; and *C*, osteoarthritis.

have shown diminished response to Concanavalin A in some but not all patients with psoriasis with or without arthritis [12–16]. Defective immunoregulatory cell activity has recently been reported in patients with psoriasis. Sauder et al [9], using Concanavalin to induce suppression of mitogen responsiveness demonstrated a marked impairment in suppressor cell activity in 10 patients with extensive cutaneous psoriasis. Hunyadi et al [10] using a similar assay showed impaired suppression in a group of 25 patients with psoriasis vulgaris. In the present study, an antigen specific suppressor cell system was used, in which T suppressor cell activity was generated with high dose antigen (OA) to suppress the *in vitro* antibody response to the specific antigen [11]. We have demonstrated impaired suppressor cell activity in some patients with psoriasis and psoriatic arthritis.

In contrast, patients with osteoarthritis, in whom no immunologic abnormalities have been reported, demonstrated normal suppression. This is despite the fact that patients with osteoarthritis were older than our patients with psoriasis, with or without arthritis, and might have been expected to show impaired suppression as a consequence of age [22].

The mechanism responsible for the impaired suppression remains unclear. One possibility may be a reduction in the number of T cells subserving immunoregulation. This is supported by data demonstrating a reduction in the number of T cells both in patients with cutaneous psoriasis and patients with psoriatic arthritis [16,17,19]. Moreover, a reduction in the number of T cells bearing receptors for the Fc portion of IgG (Ty cells) thought to contain suppressor cell activity has recently been demonstrated in patients with psoriatic arthritis [16]. Other mechanisms might account for the impaired suppressor cell activity observed in these patients. The nonsteroidal anti-inflammatory therapy might have contributed to the observations, but there was no constant relationship between the therapy taken and the suppressor activity. Moreover, patients with osteoarthritis receiving similar medications exhibited normal suppression. Similarly, although ultraviolet light has been shown to alter lymphocyte function [23], no correlation between SCA activity and UV-light therapy could be demonstrated. Steroids absorbed from topical application might have caused impaired suppression. However, there was no correlation between SCA and either use of topical steroids or extent of skin involvement.

Excessive T- helper or intrinsic B cell reactivity might account for the observations. The magnitude of the in vitro PFC response is the result of a balance of helper and suppressor activity upon an antigen activated B cell. Indirect evidence has suggested a normal B cell population in patients with psoriasis and psoriatic arthritis. Normal B cell numbers have been noted in these patients and a normal response to Pokeweed mitogen (a T and B cell mitogen) have been reported [16,17]. Moreover, the plaque-forming cell response in the present study was essentially normal. To date, studies of helper T cell activity have not been reported. Further studies are clearly indicated to elucidate the mechanism of impaired suppression.

Although impaired suppressor cell activity has been demonstrated in the present study, only a portion of the patients exhibited a profound immunoregulatory abnormality. Thus it is conceivable that subsets of patients may be defined with different immune abnormalities. The lack of correlation with the magnitude of skin and joint involvement suggests that in the majority of patients with cutaneous psoriasis and psoriatic arthritis additional mechanisms other than defective suppressor cell activity account for the humoral immune abberations observed.

The authors wish to acknowledge the technical expertise of Mrs. D. Cane and secretarial assistance of Miss Linda Walter.

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Announcement

An international workshop on "Cell Proliferation in Psoriasis" devoted to the analysis of methodology and kinetic and biochemical mechanisms in proliferative skin disease, and to the exploitation of cell kinetics in the chemotherapy of psoriasis, will be held in Oxford, April 5–7, 1982, Further details are available from Professor N. A. Wright, Department of Histopathology, Royal Postgraduate Medical School, Ducane Road, London W12 OHS.